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Signed Stephen Hordley

Dated 9 April 2003

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GB 0225040.5

By virtue of a direction given under Section 30 of the Patents Act 1977, the application is proceeding in the name of

IONIX PHARMACEUTICALS LTD,
185 Cambridge Science Park,
Milton Road,
Cambridge,
CB4 0GA,
United Kingdom

Incorporated in the United Kingdom,

[ADP No. 08304891001]

and

WEST PHARMACEUTICAL SERVICES DRUG DELIVERY & CLINICAL RESEARCH CENTRE LTD,
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[ADP No. 07657521001]

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P01/7700 0.00-0225040.5

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Cardiff Road
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1. Your reference — P.86887 GCW

2. Patent application number *(The Patent Office will fill in this part)* — 28 OCT 2002 — 0225040.5

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Ionix Pharmaceuticals Ltd
185 Cambridge Science Park
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08304891001
Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

SECTION 30 (1977 ACT) APPLICATION FILED 27/3/03

4. Title of the invention — FORMULATION

5. Name of your agent *(if you have one)* — J.A. KEMP & CO.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Patents ADP number *(if you know it)* 00000926001

	Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number			

	Number of earlier application	Date of filing *(day / month / year)*
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a) any applicant named in part 3 is not an inventor, or
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Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application

Signature J.A. KEMP & CO. Date 28 October 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

WOODS, Geoffrey Corlett
020 7405 3292

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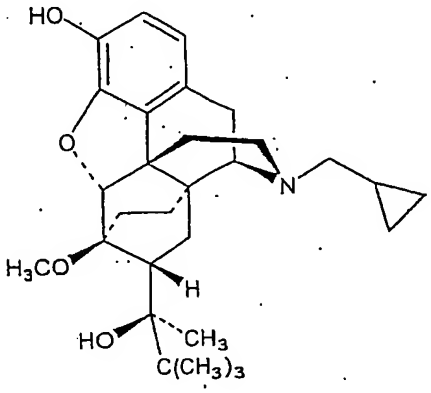
FORMULATION

The invention relates to pharmaceutical formulations of buprenorphine and physiologically acceptable salts and esters thereof.

The term opioid (or opiate) defines drugs with morphine-like properties. Opioids can be sub-classified on the basis of their receptor specificity. *Mu*-agonist opioids provide intense analgesia. These opioids can be long-acting (e.g. methadone) or short-acting (e.g. remifentanil).

Mixed agonist/antagonist opioids (e.g. butorphanol and buprenorphine) are partial agonists (the former at *mu* and kappa receptors and the latter at the *mu* receptor) and can produce good quality analgesia. They produce less respiratory depression and constipation than high efficacy *mu* agonists.

Buprenorphine (CAS RN 52485-79-7; [5α,7α(*S*)-17-(Cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol) has the formula:



The hydrochloride is also active (CAS RN 53152-21-9).

Buprenorphine is a highly lipophilic derivative of thebaine. It is a partial *mu* agonist and mediates analgesia at the *mu* opioid receptor. Buprenorphine produces a similar maximum analgesic effect to full *mu* agonists such as morphine in animal models of pain and, although it may have a ceiling effect in certain pain types in man, it has been shown to produce good quality analgesia of similar efficacy to

morphine in most clinical situations including severe pain. An unusual property of buprenorphine observed in *in vitro* studies is its very slow rate of dissociation from its receptor.

As a class, opioids are associated with a number of undesirable side-effects, including respiratory depression, nausea, vomitting, dizziness, mental clouding, dysphoria, pruritus, constipation, increased biliary tract pressure, urinary retention and hypotension. The development of tolerance and the risk of chemical dependence and abuse are further problems. Buprenorphine, however, is unusual in exhibiting a low maximum effect for respiratory depression and also a bell-shaped dose response curve where the effect first increases with larger doses, reaches a ceiling and then diminishes as the dosage is further increased, which makes it a safer drug then morphine, where respiratory depression will ultimately lead to death. Buprenorphine has also been shown to have a lower incidence of other side-effects like constipation in man, and it has a lower abuse potential than full *mu* agonists.

Buprenorphine has previously been administered via the intravenous, intramuscular and sublingual routes to human subjects. There are limited reports of nasal administration. Eriksen *et al*, J. Pharm. Pharmacol. 41, 803-805, 1989 report administration to human volunteers of a nasal spray. The spray consisted of 2mg/ml of buprenorphine hydrochloride dissolved in 5% dextrose and the pH of the solution was adjusted to pH 5.

An improved buprenorphine formulation for nasal administration has now been devised. Rapid uptake of the buprenorphine across the nasal mucosa into the plasma can be achieved, which results in fast onset of analgesia. Further, the residence time of the buprenorphine in the nasal cavity is increased, which results in prolonged analgesia. An improved profile of absorption of buprenorphine into the systemic circulation can thus be achieved by use of the formulation.

Accordingly, the present invention provides an aqueous solution suitable for intranasal administration, which comprises from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof and from 2 to 40 mg/ml of a pectin

having a degree of esterification of less than 50%; which solution has a pH of from 3 to 4.8 and is substantially free from divalent metal ions.

The invention further provides a process for the preparation of such an aqueous solution, which comprises dissolving buprenorphine or a physiologically acceptable salt or ester thereof in water; mixing the resulting solution with a solution of a said pectin in water such that the mixed solution comprises from 0.1 to 10 mg/ml of buprenorphine or said salt or ester thereof and from 2 to 40 mg/ml of the pectin; and adjusting the pH of the solution to a value from 3 to 4.8 if desired.

The invention also provides:

- a nasal delivery device loaded with a solution of the invention;
- use of a solution of the invention for the manufacture of a nasal delivery device for use in inducing analgesia; and
- a method of inducing analgesia in a patient in need thereof, which method comprises intranasally administering a solution of the invention to the patient.

The pharmaceutical solution of the invention consists essentially of 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof, from 2 to 40 mg/ml of a pectin having a low degree of esterification, in particular a degree of esterification of less than 50%, and water. The buprenorphine salt may be an acid addition salt or a salt with a base. Suitable acid addition salts include the hydrochloride, sulphate, methane sulphonate, stearate, tartrate and lactate salts. The hydrochloride salt is preferred.

The concentration of buprenorphine or buprenorphine salt or ester is from 0.1 to 10 mg/ml, for example from 0.5 to 8 mg/ml. Preferred concentrations are 1 to 6 mg/ml, for example 1 mg/ml or 4 mg/ml, calculated as buprenorphine. The solution of the invention is typically delivered as a nasal spray. A 100 µl squirt of a solution containing 1 to 4 mg/ml of buprenorphine or a buprenorphine salt or ester, calculated as buprenorphine thus results in a clinical dose of 100 to 400 µg of the buprenorphine or buprenorphine salt or ester, calculated as buprenorphine. Two such squirts may be given per nostril per administration time to deliver a dose of up to 4 x 400 µg, i.e. up

to 1600 μg, of buprenorphine or the buprenorphine salt or ester, calculated as buprenorphine.

The pectin is a gelling agent. The pectin gels on the mucosal surfaces of the nasal cavity after delivery. The buprenorphine or buprenorphine salt or ester that is formulated with the pectin is thus retained for longer on the surfaces of the nasal epithelium. The resulting sustained release of the buprenorphine or buprenorphine salt or ester into the bloodstream enables prolonged analgesia to be achieved. Improved delivery of buprenorphine or a buprenorphine salt or ester can consequently be obtained. Rapid uptake of the buprenorphine or buprenorphine salt or ester also results, which leads to fast onset of analgesia.

The solutions of the invention contain a pectin having a degree of esterification of less than 50%. A pectin is a polysaccharide substance present in the cell walls of all plant tissues. Commercially pectins are generally obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. A pectin consists of partially methoxylated polygalacturonic acids. The proportion of galacturonic acid moieties in the methyl ester form represents the degree of esterification or methoxylation, i.e. if four out of five acid groups is esterified this represents a degree of esterification of 80%. Pectins can be categorised into having a low degree of esterification (low methoxylation) or a high degree of esterification (high methoxylation). A "low DE" or "LM" pectin has a degree of esterification below 50% whereas a "high DE" or "HM" pectin has a degree of esterification of 50% or above. The gelling properties of aqueous pectin solutions can be controlled by the concentration of pectin, the type of pectin, especially the degree of esterification of the galacturonic acid units, and the presence of added salts.

Low DE pectins are used in the present invention. The primary mechanism by which such pectins gel in aqueous solution is through exposure to meal ions, such as those found in the nasal mucosal fluid. The degree of esterification of the pectin used in the invention is preferably less than 35%. The degree of esterification may thus be from 10 to 35%, for example from 15 to 25%. Low DE pectins may be

purchased commercially. An example of a low DE pectin is SLENDID (trade mark) 100, supplied by CP Kelco (Copenhagen, Denmark) which has a degree of esterification of around 10%.

The solutions of the invention must not gel on storage. They must therefore be substantially free of agents which cause pectins having a degree of esterification of less than 50% to gel. In particular, they must be substantially free of divalent metal ions and especially calcium ions. By "substantially free" of divalent metal ions we mean greater than 97%, preferably greater than 99%, more preferably greater than 99.9% and especially greater than 99.99% free.

A pectin is present in the solutions of the invention at a concentration of from 2 to 40 mg/ml, for example from 5 to 30 mg/ml. More preferably, the pectin concentration is from 10 to 25 mg/ml.

A solution of the invention has a pH of from 3 to 4.8. Any pH within this range may be employed provided the buprenorphine or buprenorphine salt or esteremains dissolved in the solution. The pH may be from 3 to 4.2, for example from 3.2 to 3.8. A suitable pH is from 3.2 to 3.6 such as from 3.3 to 3.5. The pH may be adjusted to an appropriate value by addition of a physiologically acceptable acid and/or physiologically acceptable buffer. The pH may thus be adjusted solely by means of a physiologically acceptable mineral acid or solely by means of a physiologically acceptable organic acid. The use of hydrochloric acid is preferred.

Any suitable preservative may be present in the solution, in particular a preservative that prevents microbial spoilage of the solution. The preservative may be any pharmaceutically acceptable preservative, for example phenylethyl alcohol or propyl hydroxybenzoate (propylparaben) or one of its salts. The phenylethyl alcohol and the propylparaben or propylparaben salt are preferably used in combination. The preservative must be compatible with the other components of the solution and, in particular, must not cause gelling of the solution.

Solutions of the invention may include a tonicity adjustment agent such as a sugar, for example dextrose, or a polyhydric alcohol for example mannitol. A

solution may be hypertonic, substantially isotonic or hypotonic. The osmolality of a solution may be from 0.1 to 0.8 osmol/kg such as from 0.2 to 0.6 osmol/kg or from 0.25 to 0.4 osmol/kg. A substantially isotonic solution can have an osmolality of from 0.28 to 0.32 osmol/kg. An extactly isotonic solution is 0.29 osmol/kg. A suitable osmolality range is from 0.32 to 0.36 osmol/kg. A sufficient amount of a tonicity adjustment agent such as dextrose or mannitol may therefore be present to achieve such osmolalities. Preferably a solution contains 50 mg/ml dextrose or mannitol.

A solution of the invention is prepared by dissolving buprenorphine or a physiologically acceptable salt or ester thereof in water, typically Water for Injections. The resulting solution is mixed with a solution of a suitable pectin in water, again typically Water for Injections. The amount of the buprenorphine or salt or ester thereof and of the pectin are selected so that from 0.1 to 10 mg/ml of buprenorphine or the buprenorphine salt or ester and from 2 to 40 mg/ml of pectin are dissolved in the mixed solution. A preservative or combination of preservatives may be dissolved in the solution. The pH of the mixed solution can be adjusted to from 3 to 4.8 if required. Preferably, the pH is adjusted with hydrochloric acid if pH adjustment is required.

Other components can be provided in solution at any convenient stage. For example, dextrose or mannitol may be dissolved in the water in which the buprenorphine or buprenorphine salt or ester is being dissolved. A sterile solution can be obtained either by using sterile starting materials and operating under sterile conditions and/or by passing the final solution through a sterilising filter. A pyrogen-free solution can thus be provided. The solution can then be introduced into a nasal delivery device, typically a sterile such device.

The solution of the invention is administered intranasally to a patient in need of analgesia. Rapid onset of analgesia and prolonged analgesia can thus be obtained. An effective amount of buprenorphine or a salt or ester thereof is delivered to a patient. A unit dose can be delivered to one nostril. Alternatively, half of a dose or

two doses can be delivered to each nostril each administration time. The dose will depend upon a number of factors including the age and sex of the patient, the nature and extent of the pain to be treated and the period of treatment. A suitable dose of buprenorphine or a buprenorphine salt or ester is from 0.02 to 1.2 mg, such as from 50 to 600 μg or from 100 to 400 μg, calculated as buprenorphine.

Multiple doses of a solution according to the invention may be employed. For example, the rapid onset analgesia produced by the solution of the invention may permit self-titration of analgesic by the patient. The analgesic effect of an initial dose can be quickly and reliably gauged by the patient and, if insufficient, can be immediately supplemented by further dose(s) (often alternating between each nostril) until the required level of analgesia is attained. Multiple dosing may also be used in order to extend pain relief. For example, from 2 to 4 doses per day may be indicated.

The solution of the invention may be used to treat an existing pain condition or to prevent a pain condition from occurring. An existing pain may be alleviated. Solutions of the invention can be used to treat or manage chronic or acute pain, for example the management of post-operative pain (e.g. abdominal surgery, back surgery, caesarean section, hip replacement or knee replacement).

Other medical uses include: pre-operative intranasal administration of the solution of the invention; therapy or prophylaxis adjunctive to anesthesia; post-operative analgesia; the management of trauma pain; the management of cancer pain; the management of endometriosis; the management of inflammatory pain; the management of arthritis pain (including pain associated with rheumatoid arthritis and osteoarthritis); the management of back pain; the management of myocardial pain (for example ischaemic or infarction pain); the management of dental pain; the management of neuropathic pain (e.g. diabetic neuropathy, post-herpetic neuralgia or trigeminal neuralgia); the management of colic (e.g. renal colic or gallstones), headache, migraine, fibromyalgia or dysmenorrhoea; the management of breakthrough pain associated with malignant and non-malignant disease; and the

management of acute procedural pain (e.g. bone marrow aspiration or lumbar puncture).

The solutions according to the invention may be administered to the nasal cavity in forms including drops or sprays. The preferred method of administration is using a spray device. Spray devices can be single (unit) dose or multiple dose systems, for example comprising a bottle, pump and actuator. Suitable spray devices are available from various commercial sources including Pfeiffer, Valois, Bespak and Becton-Dickinson.

As already mentioned, rapid onset of analgesia and prolonged analgesia can be achieved by means of the invention. The analgesic delivery profile that can be attained may avoid the relatively high C_{max} values associated with intravenous administration and so lead to an improved therapeutic index. The peak plasma concentration of an analgesic that is attained after administration is defined as C_{max}. The invention can permit reduction or elimination of some or all of the side effects associated with the analgesic.

In preferred embodiments, the delivery agent is adapted to deliver the analgesic component such that $C_{max} = C_{opt}$. The term C_{opt} is used in relation to analgesic drugs which exhibit a dose-response curve to analgesia which is displaced to the left with respect to the dose-response curve for side-effects. The term defines a therapeutic plasma concentration or range thereof which produces acceptable pain relief or pain amelioration but which does not produce side-effects or produces side effects which are less than those associated with higher plasma concentrations.

Preferably, the solution of the invention enables the buprenorphine or salt or ester thereof to be delivered such that C_{ther} is attained within 30 minutes (for example within 0.5 to 20 minutes such as 0.5 to 15 minutes) after introduction into the nasal cavity. The term C_{ther} defines a therapeutic plasma concentration or range thereof. Thus, the term is used herein to define a blood plasma concentration (or range of plasma concentrations) of the buprenorphine or salt or ester thereof that produces pain relief or pain amelioration.

The T_{maint} is typically from 6 to 24 hours. The term T_{maint} defines the duration of maintenance of C_{ther} after administration of the analgesic. For example, the T_{maint} can be from 7 to 12 hours, from 8 to 12 hours, from 9 to 12 hours, from 10 to 12 hours or from 11 to 12 hours.

The following Examples illustrate the invention.

Example 1: Nasal solution containing buprenorphine (4 mg/ml) and pectin

5 g of pectin (SLENDID (trade mark) 100, CP Kelco, Denmark) was dissolved by stirring into approximately 180 ml of water for injection (WFI) (Baxter, UK). 1075 mg of buprenorphine hydrochloride (MacFarlan Smith, UK) and 12.5 g of dextrose (Roquette) were dissolved into the pectin solution. 1.25 ml of phenylethyl alcohol (R. C. Treat, UK) and 50 mg of propyl hydroxybenzoate (Nipa, UK) were dissolved into the pectin/buprenorphine solution. The solution was adjusted to 250 ml using WFI.

The final product was a slightly turbid solution 4.3 mg/ml buprenorphine hydrochloride (corresponding to 4 mg/ml buprenorphine), 20 mg/ml pectin, 50 mg/ml dextrose, 5 µl/ml phenylethyl alcohol and 0.2 mg/ml propyl hydroxybenzoate.

Single dose nasal spray devices (Pfeiffer, Germany) were filled with the solution. Each device was filled with 123 µl of liquid. Actuation of the device delivered a dose of 100 µl of liquid containing 400 µg of buprenorphine and 2 mg of pectin.

Example 2: Nasal solution containing buprenorphine (2 mg/ml) and pectin

5 g of pectin is dissolved by stirring into approximately 180 ml of WFI. 538 mg of buprenorphine hydrochloride and 12.5 g of dextrose are dissolved into the pectin solution. 1.25 ml of phenylethyl alcohol and 50 mg of propyl hydroxybenzoate are dissolved into the pectin/buprenorphine solution. The solution is adjusted to 250 ml using WFI.

The final product is a slightly turbid solution containing 2.16 mg/ml

buprenorphine hydrochloride (corresonding to 2 mg/ml buprenorphine), 20 mg/ml pectin, 50 mg/ml dextrose, 5 µl/ml phenylmethyl alcohol and 0.2 mg/ml propyl hydroxybenzoate.

123 µl of the above solution is filled into a Valois Monospray single dose nasal spray device (Pfeiffer,Germany). Actuation of the device will deliver a dose of 100 µl of liquid containing 200 µg of buprenorphine and 2 mg of pectin.

CLAIMS

1. An aqueous solution suitable for intranasal administration, which comprises from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof and from 2 to 40 mg/ml of a pectin having a degree of esterification of less than 50%; which solution has a pH of from 3 to 4.8 and is substantially free from divalent metal ions.

2. A solution according to claim 1, wherein the buprenorphine or buprenorphine salt or ester is present in an amount of from 0.5 to 8 mg/ml.

3. A solution according to claim 2, wherein the buprenorphine or buprenorphine salt or ester is present in an amount of from 1 to 6 mg/ml calculated as buprenorphine.

4. A solution according to any one of the preceding claims, which comprises buprenorphine hydrochloride.

5. A solution according to any one of the preceding claims, wherein the pectin is present in an amount of from 10 to 25 mg/ml.

6. A solution according to any one of the preceding claims, wherein the pectin has a degree of esterification from 10 to 35%.

7. A solution according to any one of the preceding claims, wherein the pH is from 3.2 to 3.8.

8. A solution according to any one of the preceding claims, wherein the pH has been adjusted by means of hydrochloric acid.

9. A solution according to any one of the preceding claims, which comprises a preservative.

10. A solution according to claim 9, which comprises phenylethyl alcohol and propyl hydroxybenzoate as preservatives.

11. A solution according to any one of the preceding claims, which has an osmolality of from 0.25 to 0.4 osmol/kg.

12. A solution according to any one of the preceding claims, which contains dextrose as a tonicity adjustment agent.

13. A process for the preparation of an aqueous solution as defined in claim 1, which process comprises dissolving buprenorphine or a physiologically acceptable salt or ester thereof in water; mixing the resulting solution with a solution of a pectin in water such that the mixed solution comprises from 0.1 to 10 mg/ml of buprenorphine or said salt or ester thereof and from 2 to 40 mg/ml of the pectin; and adjusting the pH of the solution to a value from 3 to 4.8 if desired.

14. A process according to claim 13, wherein the resulting solution is introduced into a nasal delivery device.

15 A nasal delivery device loaded with a solution as claimed in any one of claims 1 to 12

16. A device according to claim 15 which is a spray device.

17. Use of a solution as defined in any one of claims 1 to 12 for the manufacture of a nasal delivery device for use in inducing analgesia.

18. A method of inducing analgesia in a patient in need thereof, which method comprises intranasally administering an aqueous solution as defined in claim 1 to the patient.

ABSTRACT

FORMULATION

An aqueous formulation suitable for intranasal administration comprises from 0.1 to 10 mg/ml of buprenorphine or a physiologically acceptable salt or ester thereof and from 2 to 40 mg/ml of a pectin having a degree of esterification of less than 50%. The solution has a pH of from 3 to 4.8 and is substantially free from divalent metal ions. Such formulations can induce rapid and prolonged analgesia.